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09/498,046	02/04/2000	Sabine Neirynck	VIB-08	8244

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,046	NEIRYNCK ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-32,34 and 36-57* is/are pending in the application.

4a) Of the above claim(s) *42-45 and 47-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-32, 34, 36-41, 46, 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/15/4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

The request filed on 10/15/4 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/498046 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 26-32, 34 and 36-57 are pending. Claims 42-45 and 47-51 are withdrawn due to a non-elected invention and claims 26-32, 34, 36-41, 46 and 52-57 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 recites the limitation "the antigen" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-32, 34, 36-41, 46, and 52-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the Office action of January 15, 2004, applicant argues that the plasmid used by Heinen et al. is not a proper control for a protein vaccine. Applicant asserts that since different types of antibody titers, other than IgG, were not measured by Heinen et al., it is not clear whether the empty plasmid elicited any change to untested components in the immune system.

Applicant's arguments as well as a review of the reference have been fully considered, but are found unpersuasive. The empty plasmid used by Heinen et al. as a negative control has no similarity with the instant fusion protein obtained from one of the inventors, Sabine Neirynck. The empty plasmid does not contain any influenza virus epitope or any other feature that could possibly protect a host against influenza virus challenge. The absence of anti-influenza virus antibodies and the lack of lymphoproliferation in response to influenza virus antigens in the negative control group are clearly demonstrated in Figures 3 and 4 of Heinen et al. The control DNA clearly does not generate any significant immune responses in either category on its own. This lack of immune response is indicative that the control DNA bears no structural or functional resemblance to the constructs containing M2e administered as vaccines. A negative control is a substance that is known not to contain the ingredient under analysis. The empty plasmid of Heinen does not contain any form of M2e administered and does not generate an immune response. The absence of an IgG and a lymphoproliferative responses clearly indicates that the empty plasmid of by Heinen et al. is a proper negative control.

Regarding the lack of measurement of any other antibody titer besides IgG by Heinen et al., it is noted that the negative control and experimental constructs evaluated in Figure 31 of the instant disclosure also only measure IgG levels. Therefore, the measurement of IgG levels for

the various control and experimental constructs by Heinen et al. is viewed as sufficient. An updated search in the influenza virus art clearly demonstrates that the M2e-HBc fusion protein does not induce anti-M2 IgA antibodies, see the second paragraph of the second column on page 5604 and Figure 3C of Jegerlehner et al. (Journal of Immunology. 2004; 172: 5598-5605). Moreover, the results of Jegerlehner et al. conclude that the M2e-HBc vaccine is insufficient for yearly epidemics and is "clearly inferior to protection achieved by immunization with classical inactivated viral preparations", see the abstract.

Applicant states that the plasmid control of Heinen et al. may have elicited an immune response if it had been administered intramuscularly, as the protein vaccines had been administered.

Eliciting a different immune response possibly due to a different route of administration has been fully considered, but is unsupported. The empty control plasmid of Heinen et al. contains absolutely no feature in common with the peptide vaccine candidates. The fusion protein vaccine candidates of Heinen et al. contain M2e influenza and hepatitis B core antigens, i.e. specific immunogenic products from pathogenic viruses. In contrast, the empty negative control plasmid contains no structural or functional immunogenic product in common with the fusion protein vaccine candidates that could induce an immune response, regardless of the route of administration.

Applicant observes that the negative control of Heinen et al. caused the highest fever. Applicant states and that the difference between the negative control and the experimental groups was statistically significant and points to the caption under Figure 2. Applicant concludes that the data of Heinen et al. suggests that M2eHBc immunity reduced fevers in swine because

the temperature of the negative control group is statistically higher than M2eHBc plus adjuvant on some days and M2eHBc on one day.

A review of Figure 2 has been fully considered in view of applicant's arguments, but is found unpersuasive. It remains quite clear from the data presented in Figure 2B that the "statistically significant differences" between the negative control and the peptide vaccine candidates do not have wide margins. Applicant is correct that the negative control caused the highest fever. This is due to the fact that the negative control results in the most severe symptoms upon administration because it has no immunogenic or ameliorative properties. The "significant difference" between the means in the negative control and the vaccine candidates is slight since the value between the differences is less than five hundredths, i.e. P (probability value) of < 0.05 in the caption under Figure 2. The data in Figure 2B clearly indicates the presence of fever in all groups. Not only is fever present, but also the vaccine candidates closely shadow the temperatures observed by the negative control. If applicant's summary regarding the data of Heinen et al. is worded another way, the M2eHBc plus adjuvant is not statistically different from the negative control group on 7 out of 11 days and the M2eHBc alone is not statistically different from the negative control group on 10 out of 11 days. Therefore, it is evident that the "statistical significant difference" in the fevers observed between the negative control group and the vaccine candidates is nonexistent or slight, since when a difference is indicated, it is less than five hundredths. This narrow differential observed between the ineffective negative control and the vaccine candidates clearly indicates that the vaccine candidates are also ineffective.

Applicant further asserts that the clinical signs observed by Heinen et al. are highly subjective. Applicant bases this conclusion on the fact that Figure 2A of Heinen et al. depicts a combination of five different clinical signs, four of which are highly subjective and not reliable indicators of flu, as evidenced by Monto, cited in the previous response. Applicant also asserts that Heinen et al. do not indicate whether the measurements were performed in a blinded manner.

A review of Figure 2A and the teachings of Monto et al. in view of applicant's arguments have been fully considered, but are found unpersuasive. Applicant appears to mistake that the previous Office action equates coughing with all of the clinical signs observed by Heinen et al. To clarify, on page 14 of the previous response from applicant, it appeared that applicant was referring to coughing as being highly subjective by stating, "Further unlike body temperatures, which can be measured accurately and objectively, this second indicator is highly subjective.[6]" "This second indicator" referred to by applicant was (apparently mistaken) considered to be referring to the presence or absence of coughs as being subjective. Therefore, this was the issue that was addressed in the previous Office action and was not intended to equate coughing with the combined clinical data presented by Heinen et al., see the paragraph bridging pages 4-5 of the Office action mailed July 15, 2003.

Turning to the teachings of Monto et al., the reference provides an analysis of signs and symptoms in adults and adolescents with influenza-like illness. The illness is "defined as having fever or feverishness plus at least 2 of the following influenza-like symptoms: headache, myalgia, cough, or sore throat.", see the "Methods" section of the abstract. Monto et al. conclude that of these symptoms, the best predictors of influenza-like illness are those

demonstrating cough and fever, see the "Results", "Conclusion" and "Comment" sections. Heinen et al. also evaluate influenza-like symptoms by objective criteria, i.e. determining whether or not a subject has a fever and coughs (one of six clinical symptoms evaluated, including fever), see the first two paragraphs under "Clinical signs and virus excretion" as well as Figures 2A and 2B. Therefore Heinen et al. evaluate the two most objective criteria defined by Monto et al.

The four other clinical symptoms evaluated by Heinen et al. include direct observation of specific types of breathing, anorexia and apathy. Like coughing and the presence of fever, these symptoms are either present in a porcine subject or not, denoted by Heinen et al. as 0 if absent and 1 if present, see the bottom of page 1854, first column. Although Monto et al. do not list these symptoms as possible clinical symptoms of influenza infection, Monto et al. are evaluating humans and Heinen et al. are evaluating pigs. While some influenza symptomology between pigs and humans overlaps, not all symptoms are applicable in every species. This is clearly evident in the symptomology present in mice, which cannot cough and the majority of which may die upon mouse-adapted virus challenge. In conclusion, the objective symptoms of influenza infection in pigs include coughing, fever, labored breathing, abdominal breathing, anorexia and apathy, as evidenced by Heinen et al. Heinen et al. determine the presence or absence of these symptoms in the negative control group as well as the vaccinated groups. The conclusion obtained by the objective data of Heinen et al. is that "...clinical signs after challenge were more severe in all immunized groups compared with the control group", see the first sentence under the "Results" section and Figure 2A on page 1854.

Applicant argues that Heinen et al. may only show that a human M2e vaccine does not protect pigs challenged with a swine influenza virus. Applicant asserts that this conclusion is not relevant to the instant claims, which require that the M2e portion be from the same species of animal from which the vaccine is intended.

Applicant's arguments have been fully considered. It has been previously conceded that the difference in between swine and human influenza virus M2e protein sequences may have contributed to the lack of protective efficacy of M2eHBc fusion proteins administered by Heinen et al. However, it is noted that the M2e sequence within the DNA construct encoding M2eNP is derived from swine influenza virus strains. This construct was also found to exacerbate disease in pigs. Therefore, the difference between the human and influenza virus M2e sequences as a contributing factor for the lack of protection is only speculative in view of the teachings of Heinen et al. Jegerlehner et al. show that although the M2eHBc construct induces antibody responses against cells infected with a human influenza virus, there are no neutralizing antibodies that developed against the virus itself. The reference also demonstrates that mice immunized with inactivated influenza virus were protected against higher doses of influenza virus than those mice administered with M2eHBc. Jegerlehner et al. conclude that M2eHBc has poor protection capacity and is not suitable for use during epidemics. See Figures 2, 3, 6 and the discussion section.

Applicant submits the teachings of Fan et al., which discusses protection achieved in mice and ferrets with M2e peptide conjugates and in mice with passive monkey sera containing M2 antibody titers. Applicant asserts that the data presented by Fan et al., which reflects the current state of the art, confirms the efficacy of applicant's claimed vaccines.

A review of Fan et al. has been fully considered, but is found unpersuasive since Jegerlehner et al. provide contradictory evidence that the M2 influenza vaccine is poorly protective.

The claims are not only drawn to a human influenza fusion vaccine comprising the extracellular part of M2 from influenza virus A, but also the NB protein from human influenza virus B or the CM2 protein from human influenza virus C. Chen et al. (Vaccine. 2001; 19: 1446-1455) clearly show that NB, derived from human influenza virus B, fails to provide protection against influenza virus B, see the abstract and Table 2. Applicant has presented no working example or evidence that fusion constructs comprising NB would be protective. Therefore, one skilled in the art would doubt that fusion proteins comprising the extracellular part of influenza virus B NB would be efficacious as a vaccine. The influenza vaccine art does not provide a teaching with respect to a fusion construct comprising influenza virus C CM2 or administering CM2. The instant disclosure also does not teach a fusion construct or an efficacious vaccine comprising the extracellular portion of this protein. Since the state of the art demonstrates that the short, conserved peptides of influenza virus A and B are not efficacious as vaccines (as taught by Heinen et al., Jegerlehner et al. and Chen et al.), it is determined that the skilled artisan would doubt that the corresponding peptide present in the influenza C virus would be effective as a vaccine. For these reasons, it is determined that the skilled artisan would be unable to use the invention without an undue quantity of experimentation.

Applicant also argues that in contrast to Heinen et al., the control groups of Fan et al. were proper because they were immunized with adjuvant only. However, neither the adjuvant of Fan et al. nor the empty plasmid of Heinen et al. have any structural or functional similarity to

the influenza M2 protein administered. In addition, neither the adjuvant nor the empty plasmid contain any influenza virus epitope or any other feature that could possibly protect a host against influenza virus challenge. Therefore, the negative controls used by Fan et al. and Heinen et al., respectively, are both equivalent negative controls.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 10:00 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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